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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/686,355

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EXAMINER

DAHLE, CHUN WU

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/686,355	Applicant(s) ZENTGRAF ET AL.	
	Examiner CHUN DAHLE	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 December 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2 and 5-10 is/are pending in the application.
- 4a) Of the above claim(s) 5-10 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 2 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's Remarks, filed on December 2, 2008, is acknowledged.

Claims 3 and 4 have been previously canceled.

Claims 1, 2, and 5-10 are pending.

Claims 5-10 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on April 25, 2006.

Claims 1 and 2 are currently under consideration.

2. This Office Action is in response to Applicant's amendment to the claims and remarks filed on December 2, 2008.

The rejections of record can be found in the previous Office Actions, mailed on July 7, 2006, January 23, 2007, and July 9, 2008.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1 and 2 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The prior Office Action, mailed on July 9, 2008, states:

"The phrase "wherein said antibody binds specifically to said histidine portion but not to the non-histidine portion of the fusion polypeptide" as recited in claims 1 and 2 is not supported by the original disclosure or claim as filed.

Applicant's amendment, filed November 6, 2006, has added the above described limitation. However, applicant fails to direct support of such amendment in the instant specification and fails to assert that no new matter has been added.

The specification as filed does not provide sufficient written description of the above-mentioned "limitation". The specification does not provide sufficient support for a monoclonal antibody against a fusion polypeptide comprising histidine portion, "wherein said antibody binds specifically to said histidine portion but not to the non-histidine portion of the fusion polypeptide". The specification only discloses antibodies recognize fusion polypeptides comprising a histidine portion as well as monoclonal antibody made from clone ACC2207 that recognizes specifically histidine fusion polypeptides but not polypeptides

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without histidine portion (see second full paragraph on page 3 and Example 3 on page 6 of the instant specification); the instant claims now recite any monoclonal antibody that binds specifically to said histidine portion but not to the non-histidine portion of the fusion polypeptide, which was not clearly disclosed in the specification. Therefore, the claims represent a departure from the specification and claims originally filed. Applicant's reliance on generic disclosure (antibodies recognize fusion polypeptides comprising a histidine portion) and possibly a single of monoclonal antibody made by clone ACC 2207 do not provide sufficient direction and guidance to the features currently claimed. It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679 683 (CCPA 1972) and MPEP 2163.05."

Applicant's arguments, filed on December 2, 2008, have been fully considered but have not been found persuasive.

Applicant argues the specification discloses monoclonal antibodies interact with a fusion protein comprising a histidine tag and provides working Example 3 to demonstrate the monoclonal anti-his antibody that bind only histidine tag of the adm2 fusion protein. Thus, applicant asserts that one of skill artisan would know that the claimed monoclonal antibodies could only bind the epitope of the histidine tag that is common to all fusion proteins.

This is not found persuasive for following reasons:

In contrast to applicant's reliance on the species of monoclonal antibody made from clone ACC2207, it is noted that the single species does not provide sufficient support the features currently claimed (e.g. a monoclonal antibody that binds only histidine portion but not to the non-histidine portion of the fusion protein). Further, the disclosure of antibodies that recognizing any fusion polypeptide comprising a histidine portion (e.g. see second paragraph on page 3 of the instant specification) does not support the claimed monoclonal antibody that binds specifically to histidine portion of the fusion protein but not to the non-histidine portion of the fusion protein. Furthermore, the negative limitation (an antibody that does not bind to the non-histidine-portion of the fusion protein) does not have basis in the original disclosure because the alternative elements are not positively recited in the specification. Therefore, the limitations recited

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in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Thus, applicant's arguments have not been found persuasive.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1 and 2 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Evans et al. (Journal of Immunological Methods 1992. 156:231-238, reference on IDS submitted on December 4, 2003) in view of Randall et al. (Vaccine 1993, 11;12:1247-1252, reference on IDS submitted on December 4, 2003) and Harlow et al. (Antibodies. A Laboratory Manual. 1988. pages 139-147, reference on PTO-892 mailed on July 7, 2006) for reasons of record.

The prior Office Action, mailed on July 9, 2008, states:

"Evans et al. teach rabbit polyclonal antibodies specifically bind a metal binding peptide His-Asp-His-Asp-His (e.g. see Material and methods on pages 232-233). Evans et al. further teach that said polyclonal antibodies recognize fusion proteins comprising the metal binding peptide but does not recognize proteins lack the metal binding peptide (e.g. see page 231). Furthermore, Evans et al. teach that monoclonal and polyclonal antibodies specific to tags such as metal binding peptide are useful in

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developing detection and quantitative assays for recombinant proteins as well as tracking intracellular distribution of expressed proteins (e.g. see page 238).

The reference teachings differ from the claimed invention by not exemplifying monoclonal antibody to metal binding peptides comprising 6-18 successive histidine residues.

Randall et al. teach a metal binding peptide that has six successive histidine residues (e.g. see abstract).

Harlow et al. teach that monoclonal antibodies can be made using hybridoma technique and that the advantages of monoclonal antibodies include high specificity in binding, homogeneity, and their ability to be produced in unlimited quantities (see entire document, particularly pages 141-147).

It would thus have been obvious to one skill in art at the time of the invention to combine the elements as claimed (e.g. monoclonal antibody that binds histidine portion but does not bind non-histidine portion) by known methods of making monoclonal antibody taught by Harlow et al. and the use of metal binding peptides taught by Evans et al. with no change in their respective functions and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. Further, substitution of one known metal binding peptide His-Asp-His-Asp-His for another metal binding peptide (e.g. six successive histidine residues) would have yielded predictable results of an antibody that recognize fusion proteins comprising the metal binding peptide but does not recognize proteins lack the metal binding peptide to one of ordinary skill in the art at the time of the invention. Furthermore, given that antibodies recognize metal binding peptide are useful in developing detection and quantitative assays for recombinant proteins and for tracking intracellular distribution of proteins and there is finite number of the metal binding peptides (e.g. His-Asp-His-Asp-His and six successive histidine residues), a person of ordinary skill has good reason to pursue the known options of making monoclonal antibody to metal binding peptides including six successive histidine residues wherein the antibody does not bind non-histidine portion of the protein within his or her own technical grasp with a reasonable expectation of success."

Applicant's arguments, filed on December 2, 2008, have been fully considered but have not been found persuasive.

Applicant argues that Evans et al. shows that antibodies to metal binding peptide (mbp) cross-react with histidine tag. Applicant asserts that Evan et al. teach antibodies to mbp are unreliable due to lack of specificity. Thus, applicant argues one of skill in the art would not substitute histidine tag for mbp. Applicant argues that Randell et al. teach that the tag containing six consecutive histidine residues with additional six amino acid residues not disclosed. Thus, applicant argues that it is not clear if the antibodies taught by Randell et al. bind histidine portion of the tag or the non-histidine portion. Applicant asserts one of skill in the art would conclude histidine tag is a poor choice of antigen for developing antibodies based upon the teachings of Randell et al. Applicant argues that the combination of Evan et al. and Randell et al. teach away from the claimed antibody

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that specifically binds the histidine portion of a fusion protein but not to the non-histidine portion of the fusion protein.

This is not found persuasive for following reasons:

In response to applicant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combination of references. See MPEP 2145.

It is noted that in considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the art would be reasonably be expected to draw therefrom In re Preda, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968). See MPEP 2144.01.

Furthermore, specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY); and In re Burckel 201 USPQ 67 (CCPA). In re Burckel is cited in MPEP 716.02.

Here, Evan et al. provide clear and convincing evidence that antibodies to histidine tag of fusion proteins are useful universal tools for methods of specific detection of proteins for structure function studies wherein the methods do not depend upon the presence of any one region of the proteins to be studied (e.g. see right column on page 238). Evan et al. teach that it is feasible to develop anti-histidine tag antibody for detection and quantitation histidine tagged proteins. Randell et al teach it is advantageous to use antibodies to tagged proteins, e.g. including histidine tagged proteins for purifications (e.g. see abstract). The histidine tag taught by Radell et al. contains an array of six histidine residues; the histidine tag falls within the scope of the claimed histiding

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portion that comprises 6-8 successive histidine residues. It would thus have been obvious to one of ordinary skill in the art at the time of the invention to combine the elements as claimed (e.g. monoclonal antibody that binds histidine portion but does not bind non-histidine portion) by known methods of making monoclonal antibody with no change in their respective functions and the combination would have yielded nothing more than predictable results of a monoclonal antibody that specifically binds to histidine tag the fusion proteins to one of ordinary skill in the art.

Further, contrary to applicant's assertions, a prior art reference must be considered in its entirety. See MPEP 2141.02. Furthermore, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." See MPEP 2123. Moreover, a prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." In re Gurley, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). General skepticism of those in the art -- not amounting to teaching away -- is also "relevant and persuasive evidence" of nonobviousness. Gillette Co. v. S.C. Johnson & Son, Inc., 16 USPQ2d 1923, 1929 (Fed. Cir. 1990). In effect, "teaching away" is a more pointed and probative form of skepticism expressed in the prior art. In any case, the presence of either of these indicia gives insight into the question of obviousness. In this case, one of ordinary skill in the art would have recognized that monoclonal antibody to histidine tag is useful universal tool (e.g. for purifying histidine tagged fusion proteins) based upon the combined teachings of references. Thus, the teachings of Evan et al. and Randell et al. do not constitute teaching away from the claimed invention.

Therefore, applicant's arguments have not been found persuasive.

8. Conclusion: no claim is allowed.

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9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chun Dahle whose telephone number is 571-272-8142. The examiner can normally be reached on 8:30-5:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Eileen O'Hara can be reached 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Chun Dahle
Patent Examiner
March 11, 2009

/Maher M. Haddad/
Primary Examiner,
Art Unit 1644

